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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/730,374	12/05/2000	John A. Lust	150.188US2	7446

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/730,374	Applicant(s) Lust et al.
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 19, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-13, 15, 17, and 18* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-13, 15, 17, and 18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment received on 2/19/03 has been entered. Claims 2, 14, and 16 have been canceled. Claims 1, 3-13, 15, and 17-18 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1, 4-8, 10, 12-13, and 15 under 35 U.S.C. 112, first paragraph, for lack of written description is withdrawn in view of applicant's amendments to the claims to indicate that the polypeptide which binds CD38 is an antibody.

The rejection of pending claims 1, 3-13, 15 and 18 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained in part over claims 1, 3-11, 15, and 18 and withdrawn over claims 12-13 in view of the amendment to the claims which indicates that the CD38 binding polypeptides are antibodies. Applicant's amendments and arguments and the declaration under 1.1.32 by Dr. Lust have been fully considered but have not been found

persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below. Please note that claims 1, 3-11, and 18 have been included in this rejection based on the recitation in the preamble of the claims that the compositions are "therapeutic" compositions or "pharmaceutical "compositions in a concentration sufficient to inhibit tumor cell growth.

The applicants state that the specification does in fact provide sufficient guidance for *in vivo* use of the claimed compositions to treat disease, particularly multiple myeloma. The applicant argues that the routes and dosages of for fusion proteins and anti-CD38 antibodies was known at the time of filing, citing Marasco et al., and Garnier et al. The applicant also states that the use of antibodies that target tumor cells was considered predictable, citing Garnier, Maloney, and the declaration by Dr. Lust. In addition, the applicant argues that the declaratory evidence and the post-filing teachings of Maloney et al. demonstrate that an anti-CD38 antibody fused to protamine and complexed with a plasmid can be internalized by CD38+ cells. In response, it is noted that the declaration by Dr. Lust provides evidence that anti-CD38 antibody fused to protamine and complexed with a plasmid encoding a marker gene can be internalized by CD38+ cells *in vitro* and the marker gene expressed. However, the declaratory evidence does not provide any *in vivo* data or provide any evidence of a therapeutic effect in a mammal following the administration of a DNA immunoconjugate according to the instant invention. Marasco et al., cited against applicant's invention in a 103 rejection, see below, also teaches the *in vitro* targeting of cells with a DNA immunoconjugate. However, please note that the Marasco et al. reference

has not been applied to claim 15, and that for the purposes of art, the intended use of the compositions in the claims carries no patentable weight. If the applicant attests that the teachings of Marasco et al. are enabling for the treatment of disease, then the 103 rejection of the claims over the teachings of Marasco et al. in view of Goldmacher et al. and Ellis et al. may be applied to claim 15. In regards to the teachings of Maloney et al., this post-filing reference teaches that a fusion polypeptide comprising anti-CD38 and protamine has been produced and the experiments to determine the binding of this protein with DNA are underway. However, the article clearly states that the use of a putative anti-CD38/protamine DNA complex to target and kill CD38+ cells *in vitro* or *in vivo* has yet to be evaluated. Thus, the evidence of record only establishes the *in vitro* targeting of CD38 cells with an anti-CD38/protamine DNA complex and the expression of a marker gene in the targeted cells.

In regards to the predictability of treating myelomas with the disclosed DNA immunoconjugates, please note that the primary teachings of Maloney et al. are directed to the administration of anti-CD38 antibodies and immunotoxins to patients. It is further noted that applicant's statements that minor responses were observed in the treatment of myeloma with humanized anti-CD38 are misleading. The article on page 31 actually states that in the 4 patients who received the immunotoxin, "Although there were minor responses in paraprotein levels, none lasted for longer than 4 weeks and were not considered clinically significant" (Maloney et al., page 31, column 2, paragraph 1). In addition, Maloney et al. clearly teaches that the use of anti-CD38 immunotoxin to treat myeloma was abandoned due to attacks of acute blindness and retinal

edema in patients who received the immunotoxin. Further, unlike the instant invention, the teachings of Garnier et al. are directed to the administration of antibodies, not DNA immunoconjugates. Garnier, published in 2002, teaches that an anti-CD38 antibody was able to treat post-transplant lymphomas in patients. It is noted that the antibody used, referred to by Garnier as the Tenovus anti-CD38 was abandoned since the Tenovus anti-CD38 clone did not produce sufficient antibody. Garnier also provides evidence for the use of anti-CD20 antibodies to treat B cell malignancies. However, the instant invention concerns the treatment of tumors with anti-CD38 immunoconjugates, not the treatment of tumors with antibodies or immunotoxins. The mechanism of action of antibodies in killing tumors cells is substantially different from the use of antibodies to deliver toxins or DNA encoding toxins to cells. Garnier et al. explains that unmodified antibodies can kill target cells primarily through complement induced and antibody-dependent cellular cytotoxicity (ADCC) (Garnier, page 114-115). Complement induced cytotoxicity and ADCC are mediated by the binding of extracellular factors to the Fc region of antibodies bound to the cell. However, an immunotoxin is a fusion protein which lacks an exposed Fc region and which is designed to kill cells by delivering a toxic protein to the target cell of interest. The DNA-immunoconjugates of the instant invention are related to immunotoxins in their mode of killing. The antibody portion of the immunoconjugate is fused to a DNA binding portion. Again, the fused antibody does not have an exposed Fc region. The fusion antibody is simply supposed to target the complexed DNA which encodes the toxin to the target and mediate internalization of the complex so that the DNA can be expressed in the cell. In view of the

substantially different mechanisms of action of traditional antibodies versus immunotoxins or DNA immunoconjugates, the skilled artisan would not readily correlate the successful use of an antibody to the successful use of a DNA-immunoconjugate. Thus, a nexus does not exist between the use of anti-CD20 antibodies or a particular anti-CD38 antibody to treat tumors and applicant's methods of treating tumors using a DNA-immunoconjugate.

The previous office action stated that the specification fails to provide sufficient guidance for routes and sites of administration, dosages of the complexed vectors, and level of toxin gene expression required to effectively treat or inhibit multiple myeloma , primary amyloidosis, monoclonal gammopathy, or acute myeloid leukemia *in vivo*. Particularly in regards to route and site of administration, the specification fails to provide sufficient guidance concerning the delivery of a targeting complex, which has been locally administered, to target cells located at a distance from the site of injection. Furthermore, while the art at the time of filing proposed the use of immunotoxins to treat various conditions such as cancer, a major problem associated with the delivery of immunotoxins *in vivo* is their immunogenicity and toxicity. Delivery of foreign protein rapidly triggers natural immunity resulting in clearance of the foreign protein. For xenogeneic proteins, prexisting antibodies are often present which act quickly to clear the xenoantigens. In regards to the specific treatment of CD38+ tumors, such as multiple myeloma, the art teaches that the administration of an immunotoxin comprising an anti-CD38 antibody to patients with myeloma resulted in the generation of HAMA and toxicity induced episodes of blindness leading to the discontinuation of the treatment (Maloney et al. (1999) Sem. in Hematol., Vol. 36 (1), 30-

33, page 30). The art does not report that an any effect on the myeloma was achieved using this strategy. In addition, the art at the time of filing also teaches that the targeted delivery of nucleic acids to specific cells or tissues in vivo was considered highly unpredictable. Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). As discussed above, the specification fails to provide guidance in the form of detailed teachings or specific working examples for overcoming any of these obstacles to successful treatment of CD38+ tumors with applicant's disclosed targeting compositions.

In response to the teachings of Deonarian and Miller, the applicant argues that Deonarian discloses that many ligand/receptor systems are under investigation and that some demonstrate successful gene transfer, citing page 53 of Deonarian. However, the ligand systems used disclosed by Deonarian are not DNA-immunoconjugates according to the instant invention. Furthermore, despite progress in the field of targeted delivery, the conclusions of Deonarian are that therapeutic

targeted delivery of genes is still not predictable or routine in the art. Regarding Miller, the same holds true, while Miller does discuss some limited success in developing targeted DNA delivery systems, the author does not conclude that therapeutic targeted delivery of genes for the treatment of diseases including cancer is predictable or routine.

Finally, the applicant argues that the applicant need not disclose or teach what is well-known in the art, citing *Hybritech, Inc. v. Monoclonal Antibodies*, and that the test for enablement is whether one reasonably skilled in the art could make and use the invention without undue experimentation, *citing United States v. Telectronics, Inc.* In response, it is noted that the therapeutic use of DNA-immunoconjugates to treat cancer is not well known in the art. Further, the previous office action has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for *in vivo* use of the claimed compositions. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte*

Singh, 17 USPQ2d 1714 (BPAI 1991). Of particular relevance to the instant case, 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Therefore, in view of the art recognized unpredictability in targeting nucleic acid vectors to specific cell populations *in vivo*, the lack of guidance provided by the specification for routes of administration, dosages, etc. which correlate with any therapeutic effect on multiple myeloma or acute myeloid leukemia, the lack of *in vivo* working examples which demonstrate specific targeting of the disclosed antibody/DNA complex to CD38+ cells and expression of the encoded cytotoxic genes, the art recognized toxicity of anti-CD38 fusion proteins *in vivo* in patients, the substantial differences between antibodies and DNA-immunoconjugates as therapeutic molecules, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

The rejection of pending claims 1, 3-13, and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. in view of Goldmacher et al. , Ellis et al. and Donovan et al. , is

maintained in modified form. Based on applicant's declaration that Donovan et al. does not qualify as prior art based on its filing date and authorship, the 103 rejection has been modified by the removal of Donovan et al. as a supporting reference. Donovan et al. had previously been cited to provide another example of an anti-CD38 antibody in addition to those disclosed by Goldmacher et al. and Ellis et al. The rejection of claims 1, 3-13, and 17-18 over the combination of WO 95/22618, 10/24/95, hereafter referred to as Marasco et al., in view of Goldmacher et al. (1994) Blood, Vol. 84 (9), 3017-3025 and Ellis et al. (1995) J. Immunol., Vol. 155 (2) 925-937 still stands. Applicant's arguments regarding the teachings of Marasco et al., Goldmacher et al. and Ellis et al. have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant has described the teachings of Marasco et al., Goldmacher et al., and Ellis et al. individually and determined that each of the three references proposes a different means to target and eliminate antigen specific cells and that there is no specific teachings in these references to particularly make applicant's claimed invention. In response to applicant's arguments against the references individually, the applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, it appears that Applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches,

but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Case law dictates that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988). Note as well that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

The previous office action stated that Marasco et al. teaches methods of transforming a target cell comprising contacting a target cell with a composition comprising a single chain antibody (scFv) or Fab portion of an antibody which binds to a site on a target cell linked to a DNA binding protein such as protamine further complexed with a nucleic acid encoding a cytotoxic protein such as Pseudomonas exotoxin operably linked to a viral or cell specific promoter (Marasco et al., pages 44-46, claims 1-16, especially claims 4, 8, 9 , and 12). The h Marasco et al. further teaches the use of humanized antibodies to target cells (Marasco et al., pages 13 and 23). Marasco et al. further provides motivation for targeting tumors with said compositions by teaching that the use of the disclosed DNA-immunoconjugates allows the

delivery of cytotoxic genes to target cells such as tumors without the immunogenicity/toxicity problems associated with tradition immunotoxins (Marasco et al., pages 5, 8-9, and 13). Marasco et al. also provide motivation for choosing antibodies which target cell surface receptors which are present in large amounts on certain tumors (Marasco et al., page 13, first paragraph).

Marasco et al. only differs from the instant invention by not teaching the use of an anti-CD38 antibody, either Fab, scFV, or humanized, in order to target CD38+ tumors, e.g. multiple myeloma. Goldmacher et al. teaches an anti-CD38 immunotoxin fusion protein for the treatment of multiple myeloma wherein the anti-CD38 antibody is derived from the HB7 hybridoma (Goldmacher et al., page 3017, abstract). Goldmacher et al. further teaches that the anti-CD38 immunotoxin targets CD38+ tumor cells (Goldmacher et al., page 3017). Thus, based on the motivation provided by Marasco to use antibodies which recognize a protein overexpressed on a tumor cells in their DNA-immunoconjugate and the motivation to use the DNA-immunoconjugate system to deliver toxins to tumor cells over traditional immunotoxins, it would have been *prima facie* obvious to the skilled artisan to use the anti-CD38 antibody taught by Goldmacher in the compositions and methods taught by Marasco et al. Since Marasco et al. provides substantial guidance for how to make DNA immunoconjugates using various antibodies, and the level of skill in the art of molecular biology at the time of filing was high, the skilled artisan would have had a reasonable expectation of success in generating a DNA immunoconjugate which incorporates the anti-CD38 antibody taught by Goldmacher et al. Further, based on the successful use of the CD38 antibody to target CD38+ cells as taught by Goldmacher et al., the skilled artisan would have had

a reasonable expectation of success in using a composition comprising an anti-CD38 antibody linked to protamine and complexed with a plasmid encoding exotoxin to target the delivery of the plasmid encoding the toxin to CD38+ cells.

As noted above, Marasco et al. also teaches the use of humanized and scFV forms of an antibody as the targeting moiety of their disclosed composition. Goldmacher et al. teaches a Fab fragment of the HB7 antibody. Ellis supplements Goldmacher and Marasco by teaching a humanized anti-CD38 antibody which successfully targets and binds CD38 positive cells (Ellis et al., page 925). Based on the teachings and motivation provided by Marasco and Goldmacher above, it would have been *prima facie* obvious to use any of the anti-CD38 antibodies taught by Ellis or Goldmacher in the methods and compositions taught by Marasco et al. Further, based on the successful use of the antibodies taught by Ellis to target CD38+ cells, the skilled artisan would have had a reasonable expectation of success in making and using a composition comprising an anti-CD38 antibody which is humanized linked to protamine and complexed with a plasmid encoding exotoxin.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER